

Serial No. 09/135,183  
Filed: August 17, 1998

- a) hybridizing a first portion of a first label extender probe to a first portion of a target sequence;
  - b) hybridizing a second portion of said first label extender probe to a first portion of an amplifier probe;
  - c) hybridizing a first portion of a second label extender probe to a second portion of a target sequence;
  - d) hybridizing a second portion of said second label extender probe to a first portion of an amplifier probe;
  - e) hybridizing at least one amplification sequence of said amplifier probe to said first portion of at least one label probe.
- 

- C3*  
*cond*
- C4*  
*cond*
20. (Amended) A composition according to claim 1, 2, 23, or 24 wherein said second portion is not nucleic acid.
- 

#### REMARKS

Claims 1-25 are pending in the application. Claims 23-25 have been added. Claims 2-10 and 20 have been amended to depend from claims 1, 2, 23 and 24. Claims 12-19 have been amended to depend from claims 11 and 25. Support for the added claims and the amendments are found in the specification, particularly on page 11, lines 19-33 and page 12, lines 1-3.

No new matter is entered by the added claims and the amendments. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the pending claims is respectfully requested for the reasons that follow.

**Rejections under 35 U.S.C. § 101**

Claim 1 stands rejected under 35 U.S.C. § 101 for lack of patentable utility. The Patent Office contends that the claimed composition is not supported by a specific, substantial and credible utility or a well-established utility. Specifically, the Examiner argues that while an electrode comprised of self-assembled monolayer comprising conductive oligomers and capture probes satisfies the utility requirement, a composition further comprising a ETM labeled target nucleic acid lacks utility. Applicants respectfully disagree.

By way of review, the present invention is directed to a variety of compositions and methods for the recruitment of electron transfer moieties (ETMs) such as ferrocene to the surface of an electrode comprising a self-assembled monolayer (SAM) to allow the detection of target sequences. As outlined in the specification, this can be accomplished in a variety of ways. In one embodiment, the target sequence comprises the ETMs (for example, the ETMs can be attached during a PCR reaction; see Specification, page 54, lines 1-14). By forming an assay complex or hybridization complex with a capture probe on the surface of the electrode, the ETM is brought into sufficient proximity for electron transfer to occur. Alternatively, unlabeled target sequences can be used, and assay complexes comprising the capture probe, the target sequence, and a label probe comprising the ETMs can be formed, with similar results.

The Examiner's rejection appears to be that the latter composition has utility and the former does not, as "a composition for detecting a component of itself is not useful". The Applicants respectfully disagree, and point out that all assays for the detection of target analytes must, at some point, have the target analyte present to distinguish between its presence and absence. Thus, the addition of a target analyte to an assay does not make a previously "useful" composition "useless" under 35 U.S.C.

Serial No. 09/135,183  
Filed: August 17, 1998

The grounds for a proper rejection based on 35 U.S.C. § 101 is set forth in M.P.E.P. § 2107. Under the guidelines the Patent Office has the initial burden to show a *prima facie* case of lack of utility. See M.P.E.P. § 2107.02. The specification and the claims are to be reviewed from the perspective of one of ordinary skill in the art as to whether an applicant has asserted a specific and substantial, credible utility or a well-established utility. The applicant must provide only one credible assertion of specific and substantial utility for any claim to satisfy the utility requirement. Id.

The Applicants respectfully submit that those of skill in the art recognize the utility of nucleic acid assay technology, and particularly compositions comprising the assay components and the target sequence. Moreover, Applicants submit that the composition comprising electrodes of the claims and ETM labeled target sequences has numerous utilities in detecting nucleic acid sequences. For example, the composition finds use in a method for detecting a ETM labeled nucleic acid bound to a capture probe where the method involves applying an electronic input signal to the claimed composition and measuring the output signal (for example, see Specification, pages 90, lines 9-19).

When the target nucleic acids, for example PCR products, are derived from various disease related genes such as nonpolyposis colon cancer gene, the BRCA1 breast cancer gene, or Alzheimer's associated risk factor gene Apo E4, the composition comprising the electrode of the claims and labeled target sequence is useful in diagnostic methods for detecting presence of these specific nucleic acid sequences. (Specification, page 92, lines 1-7).

Additionally, the composition is also useful in methods of screening for viral and bacterial infections in patients or bacterial contamination in water and food supplies (Specification, page 92, lines 8-25). Thus, the claimed composition comprising electrodes with self-

**Serial No. 09/135,183**  
**Filed: August 17, 1998**

assembled monolayers and capture probes and further comprising ETM labeled target sequences capable of binding captures probes has a specific, substantial, and credible utility.

Moreover, Applicants submit that the claimed composition has a well-established utility. Under M.P.E.P. § 2107.02, the claimed subject matter has a well established utility if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention.

Detection of specific nucleic acid sequences is vital in medical diagnostics, forensics, and molecular biology. Numerous methods have been developed for identifying specific nucleic acid sequences, including polymerase chain reaction, oligonucleotide mediated ligation, and Southern hybridization. These methods use various target nucleic acid probes labeled with radioactive molecules, fluorescent ligands, or enzymatic reporter molecules. With knowledge of the utility of such target probes, a person skilled in the art would immediately appreciate that a composition comprising an electrode of the claims and ETM labeled target nucleic acid sequences allows highly sensitive detection of specific nucleic acids by altering electrode properties when labeled target sequence binds to the capture probe. Furthermore, a person skilled in art would immediately appreciate that various methods available for measuring electrode characteristics (i.e. cyclic voltammetry, AC voltammetry) are applicable to the claimed compositions (Specification, page 82, line 21-32). Accordingly, the claimed electrodes and labeled target sequences have a well-established utility in addition to the asserted specific, substantial and credible utility.

In view of the foregoing, Applicants submit that the claimed composition comprising electrodes with a self-assembled monolayer and capture probes, and further comprising ETM labeled target sequences capable of binding to capture probes has patentable utility as defined

**Serial No. 09/135,183**  
**Filed: August 17, 1998**

under 35 U.S.C. § 101. Accordingly, Applicants respectfully request withdrawal of the rejection.

**Rejections under 35 U.S.C. § 112**

Claim 1 also stands rejected under 35 U.S.C. § 112, first paragraph because the Examiner finds the subject matter of the claim not supported by a credible specific and substantial asserted utility or a well-established utility. Applicants respectfully disagree.

Applicants understanding of the Examiner's rejection is that because claim 1 lacks a specific and substantial, credible utility or a well-established utility, the specification cannot have taught a person skilled in the art how to use the claimed composition. See M.P.E.P. § 2107.01. As set forth above, Applicants have established a specific, substantial, and credible utility and a well-established utility for the composition comprising electrodes of the claims and labeled target sequences. Moreover, Applicants have provided specific embodiments in the specification, such as methods of applying an electronic input signal and measuring an output signal, to fully enable a skilled artisan to use the claimed compositions (Specification, page 87-91). Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

**CONCLUSIONS**

Applicants respectfully submit that all pending claims of the above referenced application satisfy all requirements of patent ability and are in condition for allowance. Accordingly, early notification of such allowance is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the "Response and Amendment." The attached page is captioned "VERSION WITH

Serial No. 09/135,183  
Filed: August 17, 1998

MARKINGS TO SHOW CHANGES MADE." In addition, an Appendix of the pending claims is attached for the Examiner's convenience.

If after review, the Examiner feels there are further unresolved issues or determines that prosecution of the instant application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (415) 781-1989.

Respectfully submitted,  
FLEHR HOHBACH TEST  
ALBRITTON & HERBERT LLP

Dated: 10/24/01

Robin M. Silva  
Robin M. Silva, Reg. No. 38,304

Four Embarcadero Center  
Suite 3400  
San Francisco, CA 94111-4187  
Telephone: (415) 781-1989

1062295.co

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

3. (Amended) A composition according to claim [2] 1, 2, 23, or 24 wherein said ETM is ferrocene.
4. (Amended) A composition according to claim [2] 1, 2, 23, or 24 wherein said label probe comprises a plurality of ETMs.
5. (Amended) A composition according to claim [2] 1, 2, 23, or 24 wherein said first portion of said label probe further comprises a covalently attached ETM.
6. (Amended) A composition according to claim [2] 1, 2, 23, or 24 wherein said assay complex comprises an amplifier probe.
7. (Amended) A composition according to claim [2] 1, 2, 23, or 24 wherein said assay complex comprises a capture extender probe.
8. (Amended) A composition according to claim [2] 1, 2, 23, or 24 wherein said monolayer further comprises insulators.
9. (Amended) A composition according to claim [2] 1, 2, 23, or 24 wherein said capture probe is attached to said electrode via a conductive oligomer.

**Serial No.** 09/135,183  
**Filed:** August 17, 1998

10. (Amended) A composition according to claim [2] 1, 2, 23, or 24 wherein said capture probe is attached to said electrode via an insulator.

12. (Amended) A method according to claim 11 or 25 wherein said label probe comprises a plurality of ETMs.

13. (Amended) A method according to claim 11 or 25 wherein said target sequence is attached to said electrode by hybridization to a capture probe.

14. (Amended) A method according to claim 11 or 25 wherein said target sequence is attached to said electrode by hybridizing a first portion of said target sequence to a first capture extender probe, and hybridizing a second portion of said first capture extender probe to a capture probe on the electrode.

15. (Amended) A method according to claim 11 or 25 wherein said target sequence is attached to said electrode by

- a) hybridizing a first portion of said target sequence to a first portion of a first capture extender probe;
- b) hybridizing a second portion of said first capture extender probe to a first portion of an capture probe on the electrode;
- c) hybridizing a second portion of said target sequence to a first portion of a second capture extender probe; and
- d) hybridizing a second portion of said second capture extender probe to a second portion of said capture probe.

16. (Amended) A method according to claim 11 or 25 wherein said label probe is attached to said target sequence by hybridizing said first portion of said label probe to a first portion of said target sequence.

17. (Amended) A method according to claim 11 or 25 wherein said label probe is attached to said target sequence by

- a) hybridizing a first portion of an amplifier probe to a first portion of said target sequence; and
- b) hybridizing at least one amplication sequence of said amplifier probe to said first portion of at least one label probe.

18. (Amended) A method according to claim 11 or 25 wherein said label probe is attached to said target sequence by

- a) hybridizing a first portion of a first label extender probe to a first portion of a target sequence;
- b) hybridizing a second portion of said first label extender probe to a first portion of an amplifier probe;
- c) hybridizing at least one amplication sequence of said amplifier probe to said first portion of at least one label probe.

19. (Amended) A method according to claim 11 or 25 wherein said label probe is attached to said target sequence by

**Serial No. 09/135,183**

**Filed: August 17, 1998**

- a) hybridizing a first portion of a first label extender probe to a first portion of a target sequence;
  - b) hybridizing a second portion of said first label extender probe to a first portion of an amplifier probe;
  - c) hybridizing a first portion of a second label extender probe to a second portion of a target sequence;
  - d) hybridizing a second portion of said second label extender probe to a first portion of an amplifier probe;
  - e) hybridizing at least one amplication sequence of said amplifier probe to said first portion of at least one label probe.
20. (Amended) A composition according to claim [2] 1, 2, 23, or 24 wherein said second portion is not nucleic acid.

**APPENDIX OF PENDING CLAIMS**

1. A composition comprising:
  - a) an electrode comprising:
    - i) a self-assembled monolayer comprising conductive oligomers; and
    - ii) a capture probe;
  - b) a target sequence comprising a first portion that is capable of hybridizing to said capture probe, and a second portion that does not hybridize to said capture probe and comprises at least one covalently attached electron transfer moiety (ETM).
2. A composition comprising:
  - a) an electrode comprising:
    - i) a self-assembled monolayer comprising conductive oligomers; and
    - ii) a capture probe;
  - b) a label probe comprising a first portion that is capable of hybridizing to a component of an assay complex, and a second portion comprising a recruitment linker that does not hybridize to a component of assay complex and comprises at least one covalently attached electron transfer moiety (ETM).
3. A composition according to claims 1, 2, 23, or 24 wherein said ETM is ferrocene.
4. A composition according to claim 1, 2, 23, or 24 wherein said label probe comprises a plurality of ETMs.

**Serial No. 09/135,183**  
**Filed: August 17, 1998**

5. A composition according to claim 1, 2, 23, or 24 wherein said first portion of said label probe further comprises a covalently attached ETM.
6. A composition according to claim 1, 2, 23, or 24 wherein said assay complex comprises an amplifier probe.
7. A composition according to claim 1, 2, 23, or 24 wherein said assay complex comprises a capture extender probe.
8. A composition according to claim 1, 2, 23, or 24 wherein said monolayer further comprises insulators.
9. A composition according to claim 1, 2, 23, or 24 wherein said capture probe is attached to said electrode via a conductive oligomer.
10. A composition according to claim 1, 2, 23, or 24 wherein said capture probe is attached to said electrode via an insulator.
11. A method of detecting a target nucleic acid sequence in a test sample comprising:
  - a) forming a hybridization complex including said target sequence and a capture probe; wherein said capture probe is on an electrode comprising a self-assembled monolayer comprising conductive oligomers;
  - b) directly or indirectly attaching at least one label probe to said target sequence to form an assay complex, wherein said label probe comprises a first portion capable of

**Serial No.** 09/135,183  
**Filed:** August 17, 1998

hybridizing to a component of said assay complex, and a second portion comprising a recruitment linker that does not hybridize to a component of said assay complex and comprises at least one covalently attached electron transfer moiety (ETM); and  
c) detecting the presence of said ETM using said electrode.

12. A method according to claim 11 or 25 wherein said label probe comprises a plurality of ETMs.

13. A method according to claim 11 or 25 wherein said target sequence is attached to said electrode by hybridization to a capture probe.

14. A method according to claim 11 wherein said target sequence is attached to said electrode by hybridizing a first portion of said target sequence to a first capture extender probe, and hybridizing a second portion of said first capture extender probe to a capture probe on the electrode.

15. A method according to claim 11 or 25 wherein said target sequence is attached to said electrode by

- a) hybridizing a first portion of said target sequence to a first portion of a first capture extender probe;
- b) hybridizing a second portion of said first capture extender probe to a first portion of an capture probe on the electrode;
- c) hybridizing a second portion of said target sequence to a first portion of a second capture extender probe; and

d) hybridizing a second portion of said second capture extender probe to a second portion of said capture probe.

16. A method according to claim 11 or 25 wherein said label probe is attached to said target sequence by hybridizing said first portion of said label probe to a first portion of said target sequence.

17. A method according to claim 11 or 25 wherein said label probe is attached to said target sequence by

- a) hybridizing a first portion of an amplifier probe to a first portion of said target sequence; and
- b) hybridizing at least one amplication sequence of said amplifier probe to said first portion of at least one label probe.

18. A method according to claim 11 or 25 wherein said label probe is attached to said target sequence by

- a) hybridizing a first portion of a first label extender probe to a first portion of a target sequence;
- b) hybridizing a second portion of said first label extender probe to a first portion of an amplifier probe;
- c) hybridizing at least one amplication sequence of said amplifier probe to said first portion of at least one label probe.

**Serial No. 09/135,183**  
**Filed: August 17, 1998**

19. A method according to claim 11 or 25 wherein said label probe is attached to said target sequence by

- a) hybridizing a first portion of a first label extender probe to a first portion of a target sequence;
- b) hybridizing a second portion of said first label extender probe to a first portion of an amplifier probe;
- c) hybridizing a first portion of a second label extender probe to a second portion of a target sequence;
- d) hybridizing a second portion of said second label extender probe to a first portion of an amplifier probe;
- e) hybridizing at least one amplication sequence of said amplifier probe to said first portion of at least one label probe.

20. A composition according to claim 1, 2, 23, or 24 wherein said second portion is not nucleic acid.

21. A composition according to claim 20 wherein said second portion is a metallocene polymer.

22. A composition according to claim 21 wherein said metallocene polymer is a ferrocene polymer.

23. A composition comprising:

- a) an electrode comprising:

- i) a self-assembled monolayer; and
    - ii) a capture probe;
  - b) a target sequence comprising a first portion that is capable of hybridizing to said capture probe, and a second portion that does not hybridize to said capture probe and comprises at least one covalently attached electron transfer moiety (ETM).
24. A composition comprising:
- a) an electrode comprising:
    - i) a self-assembled monolayer; and
    - ii) a capture probe;
  - b) a label probe comprising a first portion that is capable of hybridizing to a component of an assay complex, and a second portion comprising a recruitment linker that does not hybridize to a component of assay complex and comprises at least one covalently attached electron transfer moiety (ETM).
25. A method of detecting a target nucleic acid sequence in a test sample comprising:
- a) forming a hybridization complex including said target sequence and a capture probe; wherein said capture probe is on an electrode comprising a self-assembled monolayer;
  - b) directly or indirectly attaching at least one label probe to said target sequence to form an assay complex, wherein said label probe comprises a first portion capable of hybridizing to a component of said assay complex, and a second portion comprising a recruitment linker that does not hybridize to a component of said assay complex and comprises at least one covalently attached electron transfer moiety (ETM); and

**Serial No. 09/135,183**

**Filed: August 17, 1998**

c) detecting the presence of said ETM using said electrode.